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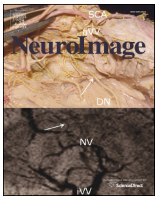

Investigating Age-related changes in fine motor control across different effectors and the impact of white matter integrity

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Changes in fine motor control that eventually compromise dexterity accompany advanced age; however there is evidence that age-related decline in motor control may not be uniform across effectors. Particularly, the role of central mechanisms in effector-specific decline has not been examined but is relevant for placing age-related motor declines into the growing literature of age-related changes in brain function. We examined sub-maximal force control across three different effectors (fingers, lips, and tongue) in 18 young and 14 older adults. In parallel with the force variability measures we examined changes in white matter structural integrity in effector-specific pathways in the brain with diffusion tensor imaging (DTI). Motor pathways for each effector were identified by using an fMRI localizer task followed by tractography to identify the fiber tracts propagating to the midbrain. Increases in force control variability were found with age in all three effectors but the effectors showed different degrees of age-related variability. Motor control changes were accompanied by a decline in white matter structural integrity with age shown by measures of fractional anisotropy and radial diffusivity. The DTI metrics appear to mediate some of the age-related declines in motor control. Our findings indicate that the structural integrity of descending motor systems may play a significant role in age-related increases in motor performance variability, but that differential age-related declines in oral and manual effectors are not likely due to structural integrity of descending motor pathways in the brain.

Introduction

In advanced age, there is a decline in the accuracy and efficiency of movements that can compromise basic dexterity for skilled movements. Although this is often suggested to reveal systemic declines in movement control, there is evidence that age-related decline in motor function varies across effectors (Enoka et al., 2003). For instance, although upper limb dexterity declines with age, the rate of decline may not be uniform across the different effectors involved in motor control and could be force level dependent (Marmon et al., 2011; Shinohara et al., 2003; Sosnoff and Voudrie, 2009). A demonstration of variation in effector control comes from work suggesting that oral motor function is better preserved than manual function in advanced age (McHenry et al., 1999).

Although few studies have compared oral versus manual motor control in aging, there appears to be a general preservation of tongue and lip force control among healthy elderly individuals without a loss of strength reserve for daily movements (Nicosia et al., 2000; Youmans and Stierwalt, 2006; Youmans et al., 2009). However, these studies have not tested oral control at low and midrange force levels at which the disproportionate decrease in force control across manual effectors has been reported in elderly participants (Enoka et al., 2003). The decline of fine manual motor control with advanced age is characterized by an increase in the amount of force variability and a decrease in variation of its temporal structure (i.e. more predictable temporal signal) (Vaillancourt and Newell, 2003). The use of the coefficient of variation (CV) and approximate entropy (ApEn) metrics enable quantification of isometric force variation and temporal complexity across both oral and manual effectors (Sosnoff and Newell, 2008).

Age-related declines in motor control have traditionally been examined by studying effectors (limbs), muscle function, and peripheral nerves (Enoka et al., 2003). More recently there has been a shift in focus to understand how changes in the CNS are related to age-related motor declines. Functional, structural, and chemical changes within the CNS have been identified that are important for understanding age-related neurological and neuromotor declines (for a recent review see Seidler et al., 2010); however the possibility of CNS changes contributing to the differential decline of effectors remains unclear. Diffusion tensor imaging (DTI), a specialized MRI technique that examines restrictions to water diffusion in the brain, has provided a platform to

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detect structural changes *in vivo*. DTI has been verified in animal models to show that the diffusion properties in a neural fiber bundle give important information about the structural integrity of specific fiber pathways (Song et al., 2002; Sun et al., 2005; Wang et al., 2011).

Two DTI measures in particular, fractional anisotropy (FA) and radial diffusivity (RD), have been used to identify correlations between age-related cognitive decline and reductions in apparent myelination in humans (Bucur et al., 2008; Madden et al., 2004, 2009; Metzler Baddeley et al., 2011). A third DTI metric, axial diffusivity (AD), has been shown to be less sensitive to age-related changes and to be better preserved in the presence of demyelination (Song et al., 2002). A commonly reported trend with age is a decrease in FA and an increase in RD, consistent with the mylodegeneration hypothesis (Davis et al., 2009). Previous studies have found pathways where DTI metrics correlate with performance on several motor control tasks (Sullivan et al., 2010; Zahr et al., 2009). These areas include the fornix, splenium, genu, and uncinate fasciculus. While these studies provide valuable insight into how motor control in the CNS changes with age, the age-related CNS changes that might occur in different effectors, such as between oral and manual effectors, have not been compared either behaviorally or with DTI methods.

In this study, white matter structural integrity within descending motor pathways (cortex to midbrain) was associated with fine force variability of oral and manual effectors in young and old adults to test whether age-related neural structural integrity changes in descending motor pathways differentiate and predict motor control changes in different effectors. Performing a low and mid-range force level control task with manual and oral effectors allowed for the assessment of differential declines in motor control at force levels that do not require maximal exertion. Specifically, oral effectors were predicted to show less prominent age-related increases in variability than manual effectors. These associated brain areas for these effectors are somatotopically organized in the motor cortex along with the descending motor pathways for these regions. We also predicted that changes in the white matter structure would correlate with performance declines, with higher age-related differences in white matter structural integrity measures in manual versus oral effectors, in agreement with age-related behavioral declines. This would correspond to a medial–lateral axis of decline across the descending motor control pathways.

Methods

Older and younger adults were recruited for participation in this study. Participants underwent two experimental sessions, one for motor control measures and one for MRI measures. For the motor control session, participants performed resultant force production tasks at low force levels using the finger, lip, and tongue. For the MRI session, the participants underwent anatomical scans and functional MRI scans to localize the finger, lip, and tongue areas followed by a diffusion imaging scan to obtain white matter structural integrity measures.

Participants

Participants were recruited to the study in accordance with the Institutional Review Board at the University of Illinois at Urbana-Champaign. Thirty-two healthy, right handed, independently living subjects participated and were divided into two groups based on age: Fourteen older subjects (8 female) between the ages of 60 and 79 years old (mean 67 years, SD 4.5 years) and 18 young participants (12 female) between the ages of 20 and 30 years old (mean 22.6 years, SD 2.0 years).

Force control measures

Each participant was seated in front of a computer monitor that displayed a static target line and a dynamic cursor controlled by force output. The participant was required to align the resultant force produced by the index finger (dominant hand), lips, or tongue (indicated by a dynamic cursor) with a visually presented static target line and maintain that force level for 25 s (similar to the procedure in Ofori et al., 2012). The task was performed 3 times for each effector (finger/lip/tongue) at 2 target force levels, 10% maximal voluntary contraction (MVC) and 20% MVC, in separate conditions. It is essentially an isometric force control task but with oral effectors that have multiple contributing muscles, use of the term 'resultant force' is more accurate (following Barlow and Muller (1991) and McHenry et al. (1999)). The resultant force data was acquired from custom-built transducers for the lip and tongue tip (Biocommunication Electronics, Madison, WI) and a load cell for the index finger (MSI Sensors, Hampton, VA) that were routed through an amplifier (Biocommunication Electronics, Madison, WI) and sampled at 100 Hz by a National Instrument A/D board. The sensitivity of each transducer was less than 0.01 Newton and visual display gain was ~256 pixels/N. The participant rested his/her forehead and chin with a head support throughout the study to minimize head motion. The lip transducer rested between the left and right angles between the upper and lower lips and essentially sampled 'inter-angle' span force or force generated by 'puckering' of the lips. The tongue transducer was controlled by upward force exerted by the tongue tip. Jaw motion during tongue contraction was further limited by forming a bite block between the upper and lower teeth with dental putty that also stabilized the tongue tip transducer. Index finger flexion force was measured by pressing down on a button transducer with the forearm stabilized on a table in front of the subject (see Ofori et al., 2012). Custom routines written in Labview (National Instruments, Austin, TX) were used to control the experiment and acquire data. Maximal voluntary contraction was determined at the beginning of the experimental procedures.

The magnitude of variability in force output was indexed using coefficient of variation (CV) and the structure of force control variability was indexed with approximate entropy (ApEn), which were determined using customized Matlab routines (Mathworks, Natick, MA, Version 2007B). CV is a measure of relative variability and is calculated as the standard deviation of a time series divided by its mean. ApEn is a measure of a time series regularity or time-dependent structure (Pincus, 1991). This measure obtains the repetition of vectors of length m and $m + 1$ that repeat in a tolerance range of r of the standard deviation of the time series. The parameters set for the calculation of ApEn values ($m = 2$ and $r = .2 \times$ standard deviation) were based on previous studies (Sosnoff and Newell, 2008). Consequently, a predictable signal (i.e. structured) such as an ideal sine wave would have a value of 0 and a signal that is not predictable (non-structured) would have a value approaching 2. A less structured signal is interpreted to be more complex (Pincus, 1991). To ensure that only continuous force production was analyzed, the first 5 s of the force signal was excluded from analysis.

Neuroimaging measures

MRI measurements were performed on a Siemens (Erlangen, Germany) Trio 3T scanner. In order to localize the finger, lip and tongue areas for determining relevant fiber tracks, participants first performed an fMRI experiment where they were instructed to activate each effector according to a visual and auditory cue. Participants were shown a picture of a finger, lips, or tongue while an auditory tone sounded at 2 Hz. Participants were instructed to tap the effector in time with the tone. Each effector was shown in four blocks and the task consisted of 10 s tapping, 14 s rest, with randomized order of effectors. The fMRI acquisition was an EPI sequence with thirty-four 3 mm thick slices with a TE of 25 ms, TR of 2 s, FOV of 220 mm, and a matrix size of 96 × 96. To aid in registration of the functional results, a T2 overlay with the same slice prescription was acquired. Additionally a high-resolution (0.9 mm isotropic) 3D T1-weighted structural scan was acquired (MPRAGE) for normalization of the participant's brain to an MNI template (Fonov et al., 2009). fMRI data processing was performed

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